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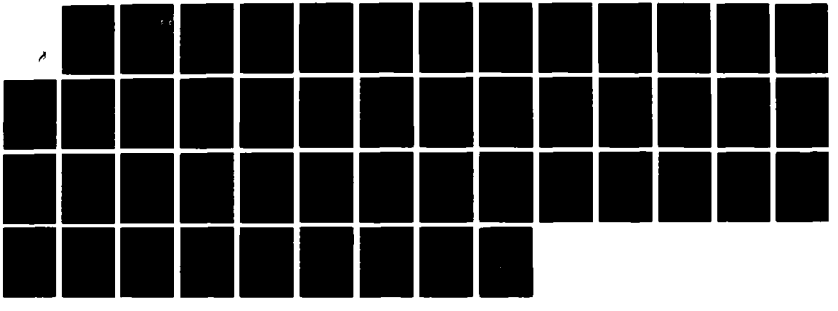

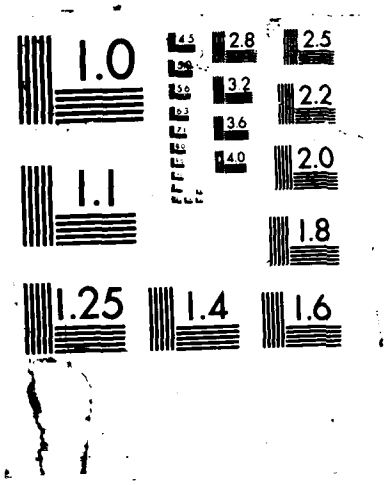
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DRUG EVALUATION IN THE PLASMODIUM FALCIPARUM-AOTUS MODEL (U)

ANNUAL REPORT

Richard N. Rossan

(For the period 1 August 1984 to 31 July 1985)

30 September 1985

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Plasmodium falciparum	blood schizonticidal drugs	acridinol
Plasmodium vivax	curative drugs	quinoline
Aotus trivirgatus	8-aminoquinoline	2-fluoral-Histidine
	acridineimine	desferrioxamine

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Infections of 2 strains of Plasmodium falciparum, Uganda Palo Alto (chloroquine sensitive) and Vietnam Smith (chloroquine resistant), or the New Guinea Chesson strain of P. vivax, in Aotus trivirgatus, were used to evaluate the blood schizonticidal and curative activity of experimental antimalarial drugs. WR 245082, an acridineimine, at a dose of 1.0 mg base per kg (x 3 days) cured infections of the Uganda Palo Alto or Vietnam Smith strain of P. falciparum. Evaluation of three 8-aminoquinolines against blood-induced infections of P. vivax indicated that WR 249420, at a dose of 1.0 mg per kg (x 3 days),

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SUMMARY

The purpose of these studies was to evaluate experimental antimalarial drugs in a non-human primate model, viz. blood-induced infections of Plasmodium falciparum or P. vivax in the owl monkey, Aotus trivirgatus. Two strains of falciparum malaria, Uganda Palo Alto (sentive to chloroquine and quinine, resistant to pyrimethamine) and Vietnam Smith (resistant to chloroquine, quinine and pyrimethamine), were used in these experiments. The strain of P. vivax was the New Guinea Chesson strain (sensitive to chloroquine, quinine and pyrimethamine).

Results of the assessment of WR 245082, an acridineimine, indicated that its curative activity against the chloroquine-sensitive and the chloroquine-resistant strain was essentially identical. Infection cures were obtained with a dose of 1.0 mg base per kg (x 3 days) in 50% of the monkeys, and a dose of 4.0 or 16.0 mg base per kg (x 3 days) cured 100% of the infections.

Three 8-aminoquinolines were evaluated for their activity against blood-induced infections of P. vivax. WR 249420, at a dose of 1.0 mg base per kg (x 3 days), cured such infections, while WR 249252 and WR 249700 were curative, each at a dose of 4.0 mg base per kg (x 3 days).

An acridinol, WR 250547, at doses of 4.0 or 16.0 mg base per kg (x 3 days) cured blood-induced infections of P. vivax.

WR 247705, a quinoline, was assessed for its activity against infections of the Uganda Palo Alto strain of P. falciparum. A dose of 4.0 mg base per kg (x 3 days) cured 50% of the infections, and a dose of 16.0 mg base per kg (x 3 days) cured 75% of the infections.

WR 251853, 2-fluoro-L-Histidine, administered intravenously at a dose of 25.0 mg base per kg (x 7 days) suppressed the parasitemia of the Uganda Palo Alto strain in 1 of 2 Aotus. A dose of 50.0 mg base per kg also suppressed the parasitemia in 2 of 2 Aotus, but both monkeys died of drug toxicity on day 6, after initiation of treatment.

WR 079520, desferrioxamine, an iron-specific chelating agent, was administered to Aotus infected with the Uganda Palo Alto strain of P. falciparum either by subcutaneous implantation of osmotic pumps or subcutaneous injection. When WR 079520 was delivered via osmotic pumps alone, the parasitemia was suppressed in 6 of 7 Aotus. Subcutaneous injection alone of desferrioxamine had no effect upon parasitemia, but when administered in conjunction with an osmotic pump implant, the parasitemia was cleared in 1 of 2 Aotus. The infection was not cured. The in vitro activity of desferrioxamine was not substantiated in vivo.

FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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EXPERIMENTAL PROCEDURES

Two monkey-adapted Plasmodium falciparum strains, Vietnam Smith (resistant to maximally tolerated doses of chloroquine, pyrimethamine, and quinine), and Uganda Palo Alto(sensitive to chloroquine and quinine, resistant to pyrimethamine) were used to induce experimental malaria infections in Aotus trivirgatus for the evaluation of the antimalarial efficacy of candidate drugs. Additionally, infections of P. vivax, Chesson (sensitive to chloroquine, pyrimethamine, and quinine), constituted a test system for some of the drugs. Infected blood, with sodium citrate (2.5%) as the anticoagulant, from untreated Aotus was diluted appropriately with chilled saline (0.85%), such that each milliliter contained 5,000,000 parasites, and this amount was injected into the saphenous vein of experimental and control monkeys.

Blood films, prepared and examined daily beginning on the first post-inoculation day, were stained with Giemsa. Parasitemias were evaluated as follows: negative, if no parasites were detected on a thick blood film after examination for at least 5 minutes; <10 parasites per cmm, if positive only on the thick blood film; parasite enumeration was by the Earle-Perez method and reported as the number of parasites per cmm.

Blood films from untreated Aotus, serving as passage and/or control subjects, were prepared and examined daily during the primary patent period, and daily thereafter for at leat three consecutive days after parasites could last be detected on thick blood films. When parasitemia had cleared, films were made and examined twice weekly until a total of 100 negative days had been recorded. If a recrudescence occurred, blood films were obtained again on a daily basis.

The schema depicted in Figure 1 represents the design of a typical drug evaluation study. Parasitemias were evaluated daily (or twice daily) during the treatment period and until blood films were negative for at least seven consecutive days. The frequency of smearing was then reduced to two times per week (Monday and Thursdays or Tuesdays and Fridays). If no recrudescences occurred during a 100 day examination period, the infection was considered to have been cured.

Drug doses were calculated as mg base per kg of body weight. Stock solution of water soluble compounds, at appropriate concentrations, were prepared with distilled water and stored at 8°C for the treatment period. If a compound was water insoluble, a suspension of the requisite amount of drug was prepared daily with 0.3% methylcellulose (in distilled water).

Oral administration of drugs was effected by gastric intubation with a 14 French catheter. The total amount of fluid administered, drug solution or suspension, and rinse was 14 ml.

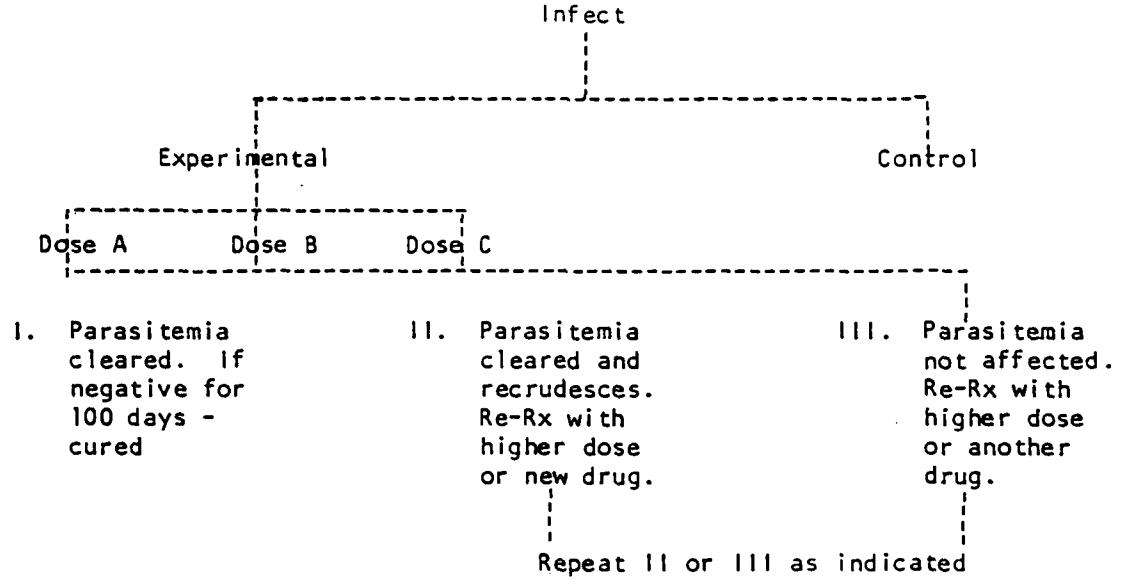
As will be indicated in subsequent sections, some drugs were administered other than by gastric intubation. In such instances, the route of drug administration was either intravenous, subcutaneous, or by implantation (subcutaneous) of one or more osmotic pumps.

FIGURE 1

SCHEMA FOR DRUG EVALUATION AGAINST

PLASMODIUM FALCIPARUM AND P. VIVAX TROPHOZOITE

INDUCED INFECTIONS IN AOTUS TRIVIRGATUS



ASSESSMENT OF THE ACTIVITY OF WR 245082AA (BN: BJ 28403) AGAINST INFECTIONS OF THE UGANDA PALO ALTO AND VIETNAM SMITH STRAINS OF PLASMODIUM FALCIPARUM

The evaluation of WR 245082, an acridineimine, against infections of the chloroquine-sensitive Uganda Falo Alto strain is indicated in Tables 1 and 3, and summarized in Table 5. Doses of 1.0, 4.0, or 16.0 mg base per kg (x 3 days) cleared primary parasitemias. All infections were cured, except in one monkey administered a dose of 1.0 mg base per kg (x 3 days). The recrudescent infection was cured with a dose of 4.0 mg base per kg (x 3 days).

Doses of 0.0625 or 0.25 mg base per kg (x 3 days) had either no effect or a only a suppressive effect on parasitemias of the chloroquine-resistant Vietnam Smith strain of P. falciparum (Tables 2,4, and 5). Parasitemias were cleared with a dose of 1.0 mg base per kg (x 3 days), and 2 of 4 primary infections were cured. This dose, however, did not cure infections in three re-treated monkeys. A dose of 4.0 mg base per kg (x 3 days) cleared parasitemias and cured 2 of 2 primary infections 3 of 5 recrudescent infections.

The infection in one Aotus was cured, after two treatment failures, with a dose of 10.0 mg base per kg (x 3 days).

Two of two primary infections and 2 of 2 recrudescences were cured with a dose of 16.0 mg base per kg (x 3 days).

CONCLUSION

The curative activity of WR 245082 against primary infections of chloroquine - sensitive and chloroquine - resistant strains was essentially identical, 50% of the infections were cured with a dose of 1.0 mg base per kg (x 3 days), and a dose of 4.0 or 16.0 mg base per kg (x 3 days) cured 100% of the infections.

TABLE 1

DETAILED ACTIVITY OF WR 245082AA (BJ 28403) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11620	1.0	0.1	2	0.6	0.4	<0.01	<0.01	<0.01	0	0	0	0
11632	1.0	0.2	1	0.3	0.2	<0.01	0	0	0	0	0	0
10840	4.0	<0.01	<0.01*	<0.01*	<0.01*	< .01	0	0	0	0	0	0
11495	4.0	0.5	5	3	0.8	<0.01	<0.01	0	0	0	0	0
11632r	4.0	3	11	4	0.3	0.1	<0.01	0	0	0	0	0
10839	16.0	0.09	1	0.5	0.09	<0.01	<0.01	<0.01	0	0	0	0
11494	16.0	0.9	3	3	1	0.1	0.06	0	0	0	0	0

* Vomited

TABLE 2

DETAILED ACTIVITY OF WR 245082AA (BJ 28403) AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
12062	0.0625	0.5	5	29	142	Re-Rx, higher dose						
12075	0.0625	0.6	10	77	417	Re-Rx, higher dose						
11600	0.25	0.1	7	3	1	0.4	0.2	1	Re-Rx, higher dose			
12077	0.25	0.4	5	6	3	2	2	1	17 Re-Rx, higher dose			
12062r	0.25	142	364	373	98	29	10	0.3	<0.01	0	0	<0.01
12075r	0.25	417	1172	950	120	442	629	476	Re-Rx, higher dose			
11693	1.0	5	9	4	2	1	<0.01	0	0	0	0	0
11699	1.0	2	46	10	1	1	<0.01	0	0	0	0	0
11665	1.0	0.7	8	4	1	0.3	<0.01	0	0	0	0	0
12068	1.0	0.4	8	3	0.5	0.1	<0.01	0	0	0	0	0
11600r	1.0	1	0.4	2	0.2	<0.01	<0.01	0	0	0	0	0
12077r	1.0	17	25	409	105	61	5	0.7	<0.01	<0.01	0	0
12062rr	1.0	0.5	2	1	1	0.3	<0.01	0	0	0	0	0
11695	4.0	4	35	5	2	1	0.3	<0.01	0	0	0	0
11812	4.0	1	2	0.6	0.2	<0.01	<0.01	0	0	0	0	0
11665r	4.0	84	471	160	20	7	0.4	<0.01	0	0	0	0
12068r	4.0	1	13	0.5	19	3	1	0.2	<0.01	0	0	0
11600rr	4.0	0.2	4	20	2	0.4	<0.01	0	0	0	0	0
12077rr	4.0	0.8	0.1	<0.01	<0.01	0	0	0	0	0	0	0
12062rrr	4.0	0.7	0.9	0.09	<0.01	<0.01	0	0	0	0	0	0
12075rr	10.0*	476	675	411	142	14	0.5	0	0	0	0	0

TABLE 2 (CONT'D.)

DETAILED ACTIVITY OF WR 245082AA (BJ 28403) AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11465	16.0	4	24	8	2	0.5	<0.01	0	0	0	0	0
11736	16.0	3	12	4	1	0.5	0.2	<0.01	0	0	0	0
12068rr	16.0	0.6	0.4	0.06	<0.01	0	0	0	0	0	0	0
12062rrrr	16.0	1	0.6	<0.01	0	0	0	0	0	0	0	0

* Incorrect dose due to technical error.

TABLE 3

SUMMARY OF THE ACTIVITY OF WR 245082AA (BJ 28403)
AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Px to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
11620	1.0			+	7	n.a.	Cured
11632	1.0			+	5	13	Re-Rx, higher dose
10840	4.0			+	5	n.a.	Cured
11495	4.0			+	6	n.a.	Cured
11632r	4.0			+	6	n.a.	Cured
10839	16.0			+	7	n.a.	Cured
11494	16.0			+	6	n.a.	Cured

TABLE 4

SUMMARY OF THE ACTIVITY OF WR 245082AA (BJ 28403)
AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Px to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
12062	0.0625	+			n.a.	n.a.	Re-Rx, higher dose
12075	0.0625	+			n.a.	n.a.	Re-Rx, higher dose
11600	0.25		+		n.a.	n.a.	Re-Rx, higher dose
12077	0.25		+		n.a.	n.a.	Re-Rx, higher dose
12062r	0.25		+		n.a.	n.a.	Re-Rx, higher dose
12075r	0.25	+			n.a.	n.a.	Re-Rx, higher dose
11693	1.0			+	6	n.a.	Cured
11699	1.0			+	7	n.a.	Cured
11665	1.0			+	6	16	Re-Rx, higher dose
12068	1.0			+	6	19	Re-Rx, higher dose
11600r	1.0			+	6	13	Re-Rx, higher dose
12077r	1.0			+	9	9	Re-Rx, higher dose
12062rr	1.0			+	6	24	Re-Rx, higher dose
11695	4.0			+	7	n.a.	Cured
11812	4.0			+	6	n.a.	Cured
11665r	4.0			+	7	n.a.	Cured
12068r	4.0			+	8	24	Re-Rx, higher dose
11600rr	4.0			+	6	n.a.	Cured
12077rr	4.0			+	4	n.a.	Cured
12062rrr	4.0			+	5	28	Re-Rx, higher dose
12075rr	10.0*			+	6	n.a.	Cured

TABLE 4 (CONT'D)

SUMMARY OF THE ACTIVITY OF WR 245082AA (BJ 28403)
AGAINST INFECTIONS OF THE VIETNAM SMITH STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Px to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
11465	16.0			+	6	n.a.	Cured
11736	16.0			+	7	n.a.	Cured
12068rr	16.0			+	4	n.a.	Cured
12062rrrr	16.0			+	3	n.a.	Cured

* Incorrect dose due to technical error.

TABLE 5

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 245082AA (BJ 28403) AGAINST TWO STRAINS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Uganda Palo Alto	3.0	1.0	2/2	1/2			2/2	1/2
	12.0	4.0	2/2	2/2	1/1	1/1	3/3	3/3
	48.0	16.0	2/2	2/2			2/2	2/2
Vietnam Smith	0.19	0.0625	0/2	0/2			0/2	0/2
	0.75	0.25	0/2	0/2	0/2	0/2	0/4	0/4
	3.0	1.0	4/4	2/4	3/3	0/3	7/7	2/7
	12.0	4.0	2/2	2/2	5/5	3/5	7/7	5/7
	30.0	10.0			1/1	1/1	1/1	1/1
	48.0	16.0	2/2	2/2	2/2	2/2	4/4	4/4

ASSESSMENT OF THE ACTIVITY OF THREE 8-AMINOQUINOLINES AGAINST BLOOD-INDUCED INFECTIONS OF THE NEW GUINEA-CHESSON STRAIN OF PLASMODIUM VIVAX

A. WR 249420AB (BN: BK 56537):

The data for the evaluation of this drug are presented in Tables 6, 7 and 8. A dose of 0.25 mg base per kg (x 3 days) suppressed the parasitemia in each of two Aotus, and retreatment with a dose of 1.0 mg base per kg (x 3 days) cured the infections. The infection in 1 of 2 Aotus was cured with a dose of 1.0 mg base per kg (x 3 days). Two of two primary infections were cured with a dose of 4.0 mg base per kg (x 3 days), and this dose cured a recrudescent infection. A dose of 16.0 mg base per kg (x 3 days) cured 2 of 2 primary infections.

B. WR 249252AA (BN: BJ 76365):

The antimalarial activity data for this 8-aminoquinoline are shown in Tables 9, 10 and 11. Primary parasitemia was suppressed only with a dose of 1.0 mg base per kg (x 3 days) in each of 2 monkeys. A dose of 4.0 mg base per kg (x 3 days) cured 1 of 2 primary infections, and 1 of 2 re-treated infections. One of 2 primary infections and 2 of 2 recrudescences were cured with a dose of 16.0 mg base per kg (x 3 days). One recrudescence was cured with a dose of 64.0 mg base per kg (x 3 days).

C. WR 249700AA (BN: BK 01676):

The data for the evaluation of this 8-aminoquinoline against P. vivax are presented Tables 12, 13, and 14. Parasitemia was suppressed only with a dose of 1.0 mg base per kg (x 3 days). A dose of 4.0 mg base per kg (x 3 days) cured 1 of 2 primary infections and 2 of 2 infections in retreated monkeys. One of two primary infections was cured with a dose of 16.0 mg base per kg (x 3 days), as was a recrudescent infection. One recrudescent infection was cured with a dose of 64.0 mg base per kg (x 3 days).

CONCLUSION

Primaquine, the only drug available for radical cure of sporozoite-induced infections of P. vivax, is essentially inactive against the Trophozoite stages of this plasmodium. The three 8-aminoquinolines evaluated against blood-induced infections of P. vivax in Aotus did cure such infections. WR 249420 achieved cure at a dose 1.0 mg base per kg (x 3 days), and WR 249252 and WR 249700 were each curative at a dose of 4.0 mg base per kg (x 3 days). The radical curative activity of these drugs has not been evaluated in Aotus.

TABLE 6

DETAILED ACTIVITY OF WR 249420AB (BK 56537) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm·x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11267	0.25	2	13	8	13	14	20	14	4	Re-Rx, higher dose		
11303	0.25	2	6	10	20	66	21	19	13	Re-Rx, higher dose		
11407	1.0	0.3	0.2	0.09	0.2	0.2	<0.01	0	0	0	0	0
11472	1.0	1	8	16	13	13	9	0.3	<0.01	<0.01	<0.01	<0.01
11267r	1.0	4	2	0.6	0.6	0.05	0.2	<0.01	0	0	0	0
11303r	1.0	13	3	2	2	0.6	0.2	0.04	<0.01	0	0	0
11231	4.0	3	42	38	27	5	0.3	0.02	0.06	<0.01	0	0
11341	4.0	3	11	20	13	2	0.1	<0.01	<0.01	0	0	0
11529	4.0	0.5	1	3	3	0.4	<0.01	0	0	DIED*		
11472r	4.0	31	15	19	4	0.3	<0.01	0	0	0	0	0
11340	16.0	7	15	27	13	2	0.5	<0.01	<0.01	<0.01	0	0
11342	16.0	3	4	13	14	1	0.3	<0.01	0	0	0	0

* Peritonitis

TABLE 7

SUMMARY OF THE ACTIVITY OF WR 249420AB (BK 56537) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
11267	0.25		+		n. a.	n.a.	Re-Rx, higher dose
11303	0.25		+		n. a.	n.a.	Re-Rx, higher dose
11407	1.0			+	6	n.a.	Cured
11472	1.0			+	11	25	Re-Rx, higher dose
11267r	1.0			+	7	n.a.	Cured
11303r	1.0			+	8	n.a.	Cured
11231	4.0			+	9	n.a.	Cured
11341	4.0			+	8	n.a.	Cured
11529	4.0			+	6	n.a.	Died Day 8 post-Rx *
11472r	4.0			+	5	n.a.	Cured
11340	16.0			+	8	n.a.	Cured
11342	16.0			+	7	n.a.	Cured

* Peritonitis

TABLE 8

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 249420AB (BK 56537) AGAINST INFECTIONS OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Chesson	0.75	0.25	0/2	0/2			0/2	0/2
	3.0	1.0	2/2	1/2	2/2	2/2	4/4	3/4
	12.0	4.0	2/2	2/2	2/2	1/1	4/4	3/3
	48.0	16.0	2/2	2/2			2/2	2/2

TABLE 9

DETAILED ACTIVITY OF WR 249252AA (BJ 76365) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11535	1.0	2	6	7	22	27	17	8	6	Re-Rx, higher dose		
11629	1.0	3	10	10	40	47	3	0.4	0.06	<0.01	<0.01	0
11475	4.0	0.9	3	3	5	3	0.2	<0.01	<0.01	<0.01	0	0
11558	4.0	1	2	3	4	0.6	<0.01	<0.01	<0.01	0	0	0
11535r	4.0	6	8	4	11	1	0.2	0.2	0.2	0.02	<0.01	0
11629r	4.0	<0.01	<0.01	0.1	0.1	<0.01	<0.01	0	0	0	0	0
11476	16.0	1	7	13	25	39	11	0.5	0.1	0.2	<0.01	<0.01
11539	16.0	2	7	15	20	21	0.6	<0.01	<0.01	<0.01	0	0
11475r	16.0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0	0	0	0	0
11535r r	16.0	0.06	0.04	<0.01	<0.01	0	0	0	0	0	0	0
11476 r	64.0	<0.01	<0.01	0	0	0	0	0	0	0	0	0

TABLE 10

SUMMARY OF THE ACTIVITY OF WR 249252AA (BJ 76365)
AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Px			Days from Initial Px to Parasite Clearance	Days from Final Px To Recrudescence	Notes
		None	Suppressed	Cleared			
11535	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11629	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11475	4.0			+	9	12	Re-Rx, higher dose
11558	4.0			+	8	n.a.	Cured
11535r	4.0			+	10	48	Re-Rx, higher dose
11629r	4.0			+	6	n.a.	Cured
11476	16.0			+	11	21	Re-Rx, higher dose
11539	16.0			+	9	n.a.	Cured
11475r	16.0			+	6	n.a.	Cured
11535rr	16.0			+	5	n.a.	Cured
11476r	64.0			+	2	n.a.	Cured

TABLE 11

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 249252AA (BJ 76365) AGAINST INFECTIONS OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Chesson	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	2/2	1/2	2/2	1/2	4/4	2/4
	48.0	16.0	2/2	1/2	2/2	2/2	4/4	3/4
	192.0	64.0			1/1	1/1	1/1	1/1

TABLE 12

DETAILED ACTIVITY OF WR 249700AA (BK 01676) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11345	1.0	1	1	2	3	3	4	4	Re-Rx, higher dose			
11718	1.0	1	4	16	9	29	10	3	Re-Rx, higher dose			
11543	4.0	2	5	13	13	6	2	0.4	0.09	<0.01	<0.01	0
11555	4.0	2	6	16	46	51	34	20	5	0.8	0.3	0.07
11345r	4.0	4	4	2	2	2	1	1	0.2	<0.01	<0.01	<0.01
11718r	4.0	3	5	4	2	1	0.5	0.05	<0.01	0	0	0
11442	16.0	1	2	12	10	27	20	16	4	3	0.8	0.9
11540	16.0	2	5	17	32	36	6	0.2	0.3	0.09	0.1	<0.01
11555r	16.0	0.06	0.2	0.08	0.5	0.2	<0.01	0	0	0	0	0
11442	64.0	0.02	0.04	<0.01	0	0	0	0	0	0	0	0

TABLE 13

SUMMARY OF THE ACTIVITY OF WR 249700AA (BK 01676)
AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recru-descence	Note
		None	Suppressed	Cleared			
11345	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11718	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11543	4.0			+	7	n.a.	Cured
11555	4.0			+	12	29	Re-Rx, higher dose
11345r	4.0			+	10	n.a.	Cured
11718r	4.0			+	7	n.a.	Cured
11442	16.0			+	13	29	Re-Rx, higher dose
11540	16.0			+	11	n.a.	Cured
11555r	16.0			+	6	n.a.	Cured
11442r	64.0			+	3	n.a.	Cured

TABLE 14

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 249700AA (BK 01676)
AGAINST INFECTIONS OF PLASMODIUM VIVAX

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Chesson	3.0	1.0	0/2	0/2			0/2	0/2
	12.0	4.0	2/2	1/2	2/2	2/2	4/4	3/4
	48.0	16.0	2/2	1/2	1/1	1/1	3/3	2/3
	192.0	64.0			1/1	1/1	1/1	1/1

ASSESSMENT OF THE ACTIVITY OF WR 250547AA (BN: BK 51630) AGAINST BLOOD-INDUCED INFECTIONS OF THE NEW-GUINEA CHESSON STRAIN OF PLASMODIUM VIVAX

The data for the antimalarial assessment of this acridinol, a stereoisomer of floxacrine, are presented in Tables 15, 16, and 17. A dose of 1.0 mg base per kg (x 3 days) cleared 3 of 4 primary P. vivax parasitemias, and cured one infection. A dose of 4.0 mg base per kg (x 3 days) cleared 4 of 4 primary parasitemias, and cured 3 of 3 of these infections. One monkey died of an intercurrent infection before cure could be ascertained. Three of three recrudescent infections were cured with a dose of 4.0 mg base per kg (x 3 days).

A dose of 16.0 mg base per kg (x 3 days) cured 3 of 4 primary infections, and a dose of 64.0 mg base per kg (x 3 days) cured the treatment failure.

CONCLUSION

Prior evaluation of WR 250547 against infections of the Vietnam Smith strain of Plasmodium falciparum showed that this drug uniformly cured infections at doses of 4.0 or 16.0 mg base per kg (x 3 days). The activity against blood-induced P. vivax infections was essentially identical, viz. cures were achieved with doses of 4.0 or 16.0 mg base per kg (x 3 days).

TABLE 15

DETAILED ACTIVITY OF WR 250547AA (BK 51630) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx	Day of Treatment			Day Post Treatment						
			1	2	3	1	2	3	4	5	6	7
11030	1.0	0.7	2	2	1	1	15	0.4	<0.01	0	0	0
11370	1.0	1	10	25	15	3	1	0.8	0.3	Re-Rx, higher dose		
11433	1.0	1	2	5	3	1	1	0.2	0.3	0.07	<0.01	<0.01
11549	1.0	2	12	30	7	4	2	1	0.7	0.7	0.3	<0.01
11127	4.0	0.8	2	8	3	1	0.9	0.4	0.5	0.3	<0.01	<0.01
11307	4.0	1	3	4	4	1	0.9	2	0.1	<0.01	<0.01	<0.01
11395	4.0	0.9	2	4	2	0.9	0.3	0.09	<0.01	<0.01	0	0
11428	4.0	0.1	0.2	0.4	0.4	<0.01	0	<0.01	0	0	0	0
11370r	4.0	0.3	0.4	0.2	0.06	<0.01	0	0	0	0	0	0
11433r	4.0	0.07	0.1	0.02	<0.01	0	0	0	0	0	0	0
11549r	4.0	0.3	2	1	0.4	<0.01	0	0	0	0	0	0
11354	16.0	1	10	5	3	0.7	0.4	0.3	0.3	0.2	0.06	<0.01
11375	16.0	0.4	7	2	2	0.8	0.5	0.2	<0.01	<0.01	0	0
11403	16.0	0.4	2	4	3	1	0.5	0.2	0.09	Re-Rx, higher dose		
11464	16.0	2	7	5	3	0.5	0.09	0.3	0.1	0.05	<0.01	<0.01
11403r	64.0	0.09	0.3	0.1	0.03	0	0	0	0	0	0	0

TABLE 16

SUMMARY OF THE ACTIVITY OF WR 250547AA (BK 51630) AGAINST INFECTIONS OF THE CHESSON STRAIN OF PLASMODIUM VIVAX

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Px to Parasite Clearance	Days from Final Rx To Recru-descence	Notes
		None	Suppressed	Cleared			
11030	1.0			+	8	n.a.	Cured
11370	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11433	1.0			+	11	28	Re-Rx, higher dose
11549	1.0			+	11	21	Re-Rx, higher dose
11127	4.0			+	11	n.a.	Cured
11307	4.0			+	12	n.a.	Cured
11395	4.0			+	9	n.a.	Died Day 32 Post-Rx*
11428	4.0			+	7	n.a.	Cured
11370r	4.0			+	4	n.a.	Cured
11433r	4.0			+	4	n.a.	Cured
11549r	4.0			+	5	n.a.	Cured
11354	16.0			+	11	n.a.	Cured
11375	16.0			+	9	n.a.	Cured
11403	16.0		+		n.a.	n.a.	Re-Rx, higher dose
11464	16.0			+	11	n.a.	Cured
11403r	64.0			+	4	n.a.	Cured

* Peritonitis

TABLE 17

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 250547AA (BK 5!630) AGAINST INFECTIONS OF PLASMODIUM VIVAX

MALARIA	DOSE (mg/kg)		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL [illegible]	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Chesson	3.0	1.0	3/4	1/4			3/4	1/4
	12.0	4.0	4/4	3/3	3/3	3/3	7/7	6/6
	48.0	16.0	3/4	3/4			3/4	3/4
	192.0	64.0			1/1	1/1	1/1	1/1

ASSESSMENT OF THE ACTIVITY OF WR 247705AB (BN: BK 57093) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

The antimalarial assessment of WR 247705, a quinoline, is indicated in Tables 18, 19 and 20. As evaluated against the chloroquine - sensitive Uganda Palo Alto strain of Plasmodium falciparum, a dose of 1.0 mg base per kg (x 3 days) suppressed the parasitemia in each of two Aotus. Retreatment with a dose 4.0 mg per kg (x 3 days) cured the infection.

Primary parasitemias were cleared in 2 of 2 monkeys with a dose of 4.0 mg base per kg (x 3 days), but the infection was not cured. Retreatment with a dose of 16.0 mg base per kg (x 3 days) cured the infection.

A dose of 16.0 mg base per kg (x 3 days) cleared 2 of 2 primary parasitemias, and cured the infection in one monkey. The recrudescent infection was cured with a dose of 64.0 mg base per kg (x 3 days).

CONCLUSION

Prior evaluation of this quinoline against chloroquine - resistant Vietnam Smith infections indicated that cures were obtained in 25% of the monkeys treated with a dose of 4.0 mg base per kg (x 3 days), and 100% of the infections were cured with a dose of 16.0 mg base per kg (x 3 days). Assessment against infections of the chloroquine - sensitive Uganda Palo Alto strain resulted in 50% infection cure with a dose of 4.0 mg base per kg (x 3 days) and a 75% infection cure with a dose of 16.0 mg base per kg (x 3 days). The activity of WR 243709 appears not to be compromised by chloroquine - resistant plasmodial strains.

TABLE 18

DETAILED ACTIVITY OF WR 247705AB (BK 57098) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3									
		Day Pre-Rx	Day of Treatment			Day Post Treatment					
			1	2	3	1	2	3	4	5	6
11616	1.0	0.6	84	181	500	111	20	0.5	0.2	<0.01	<0.01	<0.01
11622	1.0	1	37	20	176	20	2	<0.01	<0.01	<0.01	<0.01	<0.01
11731	4.0	1	71	48	132	14	0.2	<0.01	0	0	0	0
11827	4.0	0.5	60	91	130	52	0.8	<0.01	<0.01	0	0	0
11616r	4.0	4	10	25	0.3	<0.01	0	0	0	0	0	0
11622r	4.0	0.06	0.8	2	0.4	<0.01	0	0	0	0	0	0
11683	16.0	0.7	27	35	37	3	0.3	0	0	0	0	0
11729	16.0	0.6	39	27	148	21	2	<0.01	0	0	0	0
11731r	16.0	1	5	0.6	0.2	<0.01	0	0	0	0	0	0
11827r	16.0	<0.01	0.5	5	1	0.03	0	0	0	0	0	0
11729r	64.0	0.3	1	26	7	0.8	<0.01	0	0	0	0	0

TABLE 19

SUMMARY OF THE ACTIVITY OF WR 247705AB (BK 57098)
AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 3 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recurrence	Note
		None	Suppressed	Cleared			
11616	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11622	1.0		+		n.a.	n.a.	Re-Rx, higher dose
11731	4.0			+	7	23	Re-Rx, higher dose
11827	4.0			+	8	18	Re-Rx, higher dose
11616r	4.0			+	5	n.a.	Cured
11622r	4.0			+	5	n.a.	Cured
11683	16.0			+	6	n.a.	Cured
11729	16.0			+	7	19	Re-Rx, higher dose
11731r	16.0			+	5	n.a.	Cured
11827r	16.0			+	6	n.a.	Cured
11729r	64.0			+	6	n.a.	Cured

TABLE 20

SUMMARY OF THE ANTIMALARIAL ACTIVITY OF WR 247705A8 (BK 57098) AGAINST INFECTIONS OF PLASMODIUM FALCIPARUM

MALARIA	DOSE mg/kg		PRIMARY TREATMENTS		REPEAT TREATMENTS		TOTAL TREATMENTS	
STRAIN	TOTAL	DAILY	CLEARED	CURED	CLEARED	CURED	CLEARED	CURED
Uganda	3.0	1.0	0/2	0/2			0/2	0/2
Palo	12.0	4.0	2/2	0/2	2/2	2/2	4/4	2/4
Alto	48.0	16.0	2/2	1/2	2/2	2/2	4/4	3/4
	192.0	64.0			1/1	1/1	1/1	1/1

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 251853AA (BN: BK 70877) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

In vitro studies with the Malayan Camp strain of P. falciparum at another laboratory (National Institutes of Health) have shown that WR 251853, 2-fluoro-L-Histidine, will:

1. Inhibit parasite growth,

2. Inhibit knob formation of parasitized erythrocytes.

3. Inhibit the binding of the knobless parasitized erythrocytes to melanoma cells.

Knob formation, in vivo, of falciparum - infected erythrocytes is responsible for deep-vascular sequestration allowing, in part, the parasites to escape the immune mechanism.

This pilot study was designed to determine if WR 251853 could, in vivo:

1. Inhibit knob formation.

2. Inhibit sequestration of parasitized erythrocytes.

3. Suppress parasitemia and/or alter the infection course.

Also, to ascertain toxicity of WR 251853 to Aotus.

A total of 6 Aotus was inoculated, each with 5×10^6 parasites of the Uganda Palo Alto strain of P. falciparum. Beginning on day 2 post-inoculation, the drug was administered intravenously, one-half the total dose at 8:00 AM and 3:00 PM. Two Aotus served as saline-treated controls.

As indicated Tables 21 and 22, the parasitemia was suppressed in 1 of 2 Aotus that received a total dose of 25.0 mg base per kg (x 7 days). Subsequent to the termination of treatment, the parasitemia in Aotus 10836 increased, and the monkey died of a fulminating malaria infection on the fifth day. The parasitemia in Aotus 11975 was not suppressed and this animal died on day 3 after the end of treatment.

The parasitemia in each of the two Aotus that received a total daily dose of 50.0 mg base per kg was suppressed. Both animals died, on day 6 of the treatment period, with gastric and renal pathology probably attributable to drug toxicity.

Blood films and whole blood specimens, fixed for election microscopy examination, were sent to N.I.H. for evaluation of knob formation inhibition and sequestration of parasitized erythrocytes. These results are unknown.

CONCLUSION

The suppressive activity of WR 251853, at a dose of 25.0 mg base per kg (x 7 days), was apparent in one Aotus during the course of treatment. After drug administration was terminated, the parasitemia increased, resulting in the death of the monkey. A dose of 50.0 mg base per kg suppressed the parasitemia below that of the untreated controls, but the dose was toxic, as both monkeys died on day 6 of treatment.

Further trials with this drug are not projected.

TABLE 21

DETAILED ACTIVITY OF WR 251853AA (BK 70877) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx		Day of Treatment							Day Post Treatment		
				1	2	3	4	5	6	7	1	2	3
10836	25.0*	<0.1	A.M.	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	3	1	15	115
			P.M.	<0.01	<0.01	<0.01	<0.01	<0.01	0.2	2			
11975	25.0*	<0.01	A.M.	0.8	2	15	107	195	710	309	1004	710	DIED(a)
			P.M.	0.2	17	2	160	129	959	524			
11680	50.0*	<0.01	A.M.	<0.01	<0.01	<0.01	0	0	DIED(b)				
			P.M.	<0.01	<0.01	0	0	0					
11681	50.0*	<0.01	A.M.	1	1	18	3	15	DIED(b)				
			P.M.	0.4	38	19	10	36					

* One-half total daily dose administered intravenously at 8:00 A.M. and 3:00 P.M.

a) Malaria

b) Possible drug toxicity

TABLE 22

SUMMARY OF THE ACTIVITY OF WR 251853AA (BK 70877) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose x 7 Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
10836	25.0*		+		n.a.	n.a.	
11975	25.0*	+			n.a.	n.a.	Died Day 3 post-Rx, malaria
11680	50.0*		+		n.a.	n.a.	Died Day 6 in Rx. Drug toxicity?
11681	50.0*		+		n.a.	n.a.	Died Day 6 in Rx. Drug toxicity?

* One-half total daily dose administered intravenously at 8:00 A.M. and 3:00 P.M.

ASSESSMENT OF THE ANTIMALARIAL ACTIVITY OF WR 079520AB (BN: BK 70813) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

WR 079520 is an iron - specific chelating agent, desferrioxamine. Diverse studies at other laboratories have shown that this and other iron chelating agents will inhibit (in vitro) the growth of P. falciparum. The in vivo evaluation of desferrioxamine was undertaken in collaboration with Dr. Simeon Pollack, Albert Einstein College of Medicine, Bronx, New York.

Because desferrioxamine is absorbed poorly following oral administration, the drug was delivered by subcutaneous implantation of ALZET^{R} osmotic pumps, containing 2.0 ml of a 200 mg per ml solution of desferrioxamine. As will be discussed in the appropriate section, desferrioxamine also was administered subcutaneously. The data derived from three experiments are detailed in Table 23 and summarized in Table 24. The protocol for the three experiments will be presented individually.

Experiment I:

Five Aotus were inoculated intravenously each with 5×10^6 parasites of the Uganda Palo Alto strain of P. falciparum. Two of those monkeys served as untreated controls. On day 2 after inoculation when parasites were demostrable only on thick blood films, one osmotic pump (2.0 ml of a 200 mg per ml solution of desferrioxamine) was implanted into each of three Aotus (11623, 11718, and 11719).

The pumps were in place for 10 days and, during this time, the parasitemia was suppressed in 2 of 3 monkeys. Aotus 11719, in which the parasitemia was not suppressed, died on the second day after pump removal.

Experiment II:

For this evaluation, five Aotus were inoculated intravenously each with 10×10^6 parasites. On the third day post-inoculation, two Aotus (11523 and 11531) each were implanted with two osmotic pumps (2.0 ml of a 200 mg per ml solution of desferrioxamine) subcutaneously. The parasitemia at the time of implant was 171,000 and 2,000 per cmm, respectively. Two Aotus were implanted with osmotic pumps containing 0.85% saline, and one monkey served as a third control, i.e. without osmotic pumps.

The parasitemia in the two Aotus that were administered desferrioxamine was suppressed in comparison to the untreated controls. Aotus 11523 died of peritonitis on day 5 after pump implantation, and Aotus 11531 died on day 7 following pump implantation, probably due to drug toxicity. The two Aotus that received saline pumps died of malaria on day 7 after implantation, while the third control died of malaria one day later.

Experiment III:

The protocol for this study was designed to repeat some elements of the above two experiments, but added sequential pump implantation and subcutaneous administration of desferrioxamine, alone and in conjunction with osmotic pumps.

Twelve Aotus were inoculated intravenously each with 5×10^6 parasites of the Uganda Palo Alto strain of P. falciparum. On day 2 after inoculation, when parasites were demonstrable only on thick films (Table 23), the monkeys were separated into groups and treated as follows:

Aotus 11584 and Aotus 11673 were implanted with one osmotic pump each containing 2.0 ml of a 200 mg per ml solution of desferrioxamine. During the subsequent 7 days, the parasitemia was suppressed in both monkeys. The pumps were removed on day 8 after implantation. Aotus 11584 died of malaria on the seventh day thereafter, and Aotus 11673 had a self-curative infection.

Aotus 11091 and Aotus 11098 were implanted each with one osmotic pump, as above. The parasitemia was suppressed in Aotus 11091, but not in Aotus 11098. On day 8 after pump implantation, the pumps were removed from each monkey and replaced with a new pump, containing 2.0 ml of a 200 mg per ml solution of desferrioxamine. Both monkeys died of malaria on day 6 and 3, respectively, after insertion of the new pump.

Aotus 11528 and Aotus 11599, beginning on day 2 after parasite inoculation, were injected (subcutaneously) with desferrioxamine at a dose of 30.0 mg base per kg, twice daily, for 10 consecutive days. The parasitemia was not suppressed in these two monkeys, and Aotus 11599 died of malaria on day 2 after termination of treatment. The infection in Aotus 11528 proceeded to self-cure.

Aotus 11732 and Aotus 11753 were implanted each with a single osmotic pump (2.0 ml of a 200 mg per ml solution of desferrioxamine) on day 2 after parasite inoculation plus injected subcutaneously with 30.0 mg base per kg (twice daily) of desferrioxamine. The pumps were removed on day 8 after implantation, while the drug was injected for a total of 10 consecutive days. The parasitemia in Aotus 11732 was cleared on day 4 after initiation of treatment, but a recrudescence occurred on day 5 after the last injection of desferrioxamine. The parasitemia in Aotus 11753 was suppressed, but did not clear during the treatment period.

Two of two saline-treated Aotus died of malaria, as did 1 of 2 untreated controls, on days 13, 15, 12 respectively, after pump implantation in the treated monkeys.

CONCLUSION

In vivo evaluation of an iron-specific chelating agent, desferrioxamine, against P. falciparum infections in Aotus has shown that:

1. Implantation of a single osmotic pump, containing 400 mg of desferrioxamine, suppressed the parasitemia in 4 of 5 monkeys.

2. Parasitemia was suppressed in 2 of 2 monkeys that were implanted each with two osmotic pumps. (total of 800 mg of desferrioxamine).

3. Insertion of a new pump, on day 8 after the first implantation, when the parasitemia was about 300,000 per cmm had no effect upon parasite multiplication and the monkeys died of malaria.

4. Subcutaneous administration of desferrioxamine had no effect upon parasite development in each of two Aotus.

5. Desferrioxamine, when administered by subcutaneous injection and by one osmotic pump, did clear the parasitemia in 1 of 2 Aotus. The infection, however, was not cured.

The in vitro antimalarial activity of desferrioxamine was not confirmed in vivo against a virulent strain of P. falciparum in Aotus.

TABLE 23

DETAILED ACTIVITY OF WR 079520AB (BK 70813) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3										
		Day Pre-Rx		Day of Treatment								
				1	2	3	4	5	6	7	8	9	10
11623	a.	<0.01	A.M.	<0.01	2	8	82	60	275	197	85	3	3 b
			P.M.						209	51	27	15	2
11718	a.	<0.01	A.M.	<0.01	4	13	60	88	346	346	187	14	38 b
			P.M.						284	417	151	51	95
11719	a.	<0.01	A.M.	<0.01	3	14	328	231	924	976	790	408	329 b
			P.M.						1137	1307	640	320	462
11523	c.	1	A.M.	171	76	402	223	DIED - Peritonitis					
			P.M.	189	104	163	251						
11531	c.	<0.01	A.M.	2	19	106	49	84	42	DIED - Possible drug toxicity			
			P.M.	13	14	69	39	60					

a. One osmotic pump with 2 ml of a 200 mg/ml solution
b. Pump removed
c. Two osmotic pumps each with 2 ml of a 200 mg/ml solution

TABLE 23 (CONT'D)

DETAILED ACTIVITY OF WR 079520AB (BK 70813) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Aotus No.	Daily Dose Mg/Kg	Parasitemia per cmm x 10^3									
		Day Pre-Rx	Day of Treatment							Day Post Treatment		
			1	2	3	4	5	6	7	1	2	3
11584	a.	<0.01	<0.01	1	3	25	3	51	127	17c	541	17
11673	a.	<0.01	<0.01	1	0.9	9	3	17	62	36c	280	284
11091	a.	<0.01	<0.01	0.7	2	62	118	82	302	284c	New pump	
11098	a.	<0.01	<0.01	4	8	153	157	604	921	329c	New pump	
11091r	a.	302	284	1101	959	382	570	959	DIED - MALARIA			
11098r	a.	921	329	1314	1163	DIED - MALARIA						
11528	b.	<0.01	<0.01	1	3	164	130	710	781	639Rx	408Rx	746Rx
11599	b.	<0.01	<0.01	0.7	3	240	213	293	337	781Rx	427Rx	515Rx
11732	a,b.	<0.01	<0.01	0.2	0.03	0	0	0	0	0c.Rx	0 Rx	0 Rx
11753	a,b.	<0.01	<0.01	2	1	3	1	4	5	2C.Rx	5 Rx	3 Rx

a. One osmotic pump with 2 ml of a 200 mg per ml solution.
b. 30.0 mg/kg, 2x/day, subcutaneously, for 10 consecutive days.
c. Pump removed.

TABLE 24

SUMMARY OF THE ACTIVITY OF WR 079520AB (BK 70813) AGAINST INFECTIONS OF THE UGANDA PALO ALTO STRAIN OF PLASMODIUM FALCIPARUM

Monkey No.	Daily Dose Mg/Kg	Response of Parasitemia to Rx			Days from Initial Rx to Parasite Clearance	Days from Final Rx To Recrudescence	Notes
		None	Suppressed	Cleared			
11623	a.		±		n. a.	n.a.	Died Day 2 after pump removal
11718	a.		±		n. a.	n.a.	
11719	a.	+			n. a.	n.a.	Died Day 2 after pump removal-malaria
11523	b.		±		n. a.	n.a.	Died Day 5 after pump implants-peritonitis
11531	b.		±		n. a.	n.a.	Died Day 7 after pump implants-toxici
11584	a.		+		n. a.	n.a.	Died Day 7 after pump removal-malaria
11673	a.		+		n. a.	n.a.	
11091	a.		+		n. a.	n.a.	New pump implanted
11098	a.	+			n. a.	n.a.	New pump implanted
11091r	a.	+			n. a.	n.a.	Died Day 6 after pump implant-malaria
11098r	a.	+			n. a.	n.a.	Died Day 3 after pump implant-malaria
11528	c.	+			n. a.	n.a.	
11599	c.	+			n. a.	n.a.	Died Day 2 post-Rx, malaria
11732	a,c.			+	4	5	
11753	a,c.		+		n.a.	n.a.	

a. One osmotic pump with 2 ml of a 200 mg/ml solution.
b. Two osmotic pumps each with 2 ml of a 200 mg/ml solution.
c. 30.0 mg/kg, 2x/day, subcutaneously, for 10 consecutive days.

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